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ORIGINAL ARTICLE

Studies on condensation of 1,3-dicarbonyls with malononitrile: Synthesis of 2-pyridinones

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KEYWORDS

1,3-Dicarbonyls;
Malononitrile;
2-Pyridinones;
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Cycloaddition and isomerization

Abstract A simple and novel method to the chemoselective synthesis of 3-cyano-2-pyridinone derivatives from a Knoevenagel condensation of malononitrile with the carbonyl group of 1,3-dicarbonyls followed by cycloaddition and isomerization, is reported. The reactions occur in ethanol and water at reflux, in the presence of a base catalyst such as triethylamine. This method provides an easy route to prepare 2-pyridinone derivatives in good to excellent yields and in a short experimental time.

1. Introduction

The development of heterocyclic compounds such as pyridinones is a topic of current interest because of their presence in numerous natural products along with the wide spectrum of physiological activities displayed by this class of compounds (Nagarajan et al., 2003; Fassihi et al., 2009; Manna et al., 1992). It is well known that the 2-pyridinone derivatives are valuable building blocks in natural product synthesis and also a versatile synthon for the synthesis of a variety of other nitrogen-containing heterocyclic compounds, such as β-lactams, quinolizidines, pyridines, piperidines, and indolizidine alkaloids (Elbein and Molyneux, 1981). The diene portion of these molecules can undergo Diels–Alder cycloaddition reactions with dienophiles, or one double bond may act as a dienophile to an added diene (Chou and Chen, 2008). So they have been applied as a key synthetic intermediate to synthesize some complex natural products (Snider and Che, 2004; Chen et al., 2010). A large number of methods have been developed for the synthesis of 2-pyridinones and their derivatives (Torres et al., 2005). The most common strategies involve the construction of the heterocyclic compounds from easily available starting materials. Due to the importance of 2-pyridinone skeleton, to develop new and efficient methodologies for diversely functionalized construction of 2-pyridinone is still highly desired. Organic fluorine compounds have received significant attention in the materials and pharmaceutical sciences due to their unique physical and biological properties such as the increased membrane permeability, enhanced hydrophobic binding and stability against metabolic oxidation (Kuznetsova et al., 2004; Filler et al., 1993; Chambers, 2004; Ryckmanns et al., 2002; Purser and Moore, 2008). The replacement of hydrogen by fluorine in organic molecules has frequently led to dramatic changes in their dipole moments, acidity or basicity of neighboring groups; any of which can affect molecular interactions with receptors or other interacting molecules (Muller et al., 2007). Therefore, the synthesis of fluorinated molecules plays an important role in drug discovery and many pharmaceuticals, such as well known ciprofloxacin,

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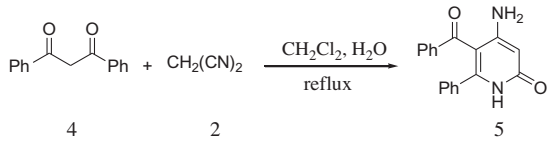
ofloxacin or norfloxacin which all contain fluorine atoms (Albrecht et al., 1994; Song et al., 1997; Popp et al., 1994; Lam et al., 2001). In continuing our previous works on the reaction of 1,3-dicarbonyls with electrophiles such as acyl ketenes (Cantillo et al., 2012; Sheibani et al., 2006a,b; Sheibani et al., 2004), arylidenemalononitrile and the S–S-bond of 2,2'-disulfanediyldianiline (Seifi and Sheibani, 2008; Sheibani et al., 2006a,b), we now turn our attention to the reactivity of malononitrile on the fluorinated-1,3-dicarbonyls to the synthesis of fluorinated-2-pyridinone derivatives. The simplicity and efficient one-pot procedure is one aspect of particular interest, in comparison to the other multi-step methods. On the other hand, readily available starting materials such as malononitrile and fluorinated-1,3-dicarbonyls, shorten experimental times, and high yield of the final products are the other advantages of this method.

2. Results and discussion

In continuing our interest in the synthesis of heterocyclic compounds which contain the 2(1H)-pyridinone skeleton (Abaszadeh et al., 2009; Sheibani et al., 2009), as exhibited in Scheme 1 the 3-cyano-2-pyridinone derivatives **(3a–e)** were prepared in the reaction of 1,3-dicarbonyl compounds (1a-e) with malononitrile **2** followed by cycloaddition and isomerization in good to excellent yields and in a short experimental time.

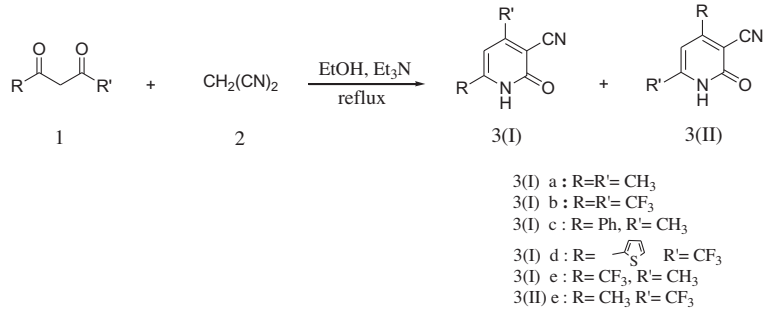
Unsymmetrical 1,3-diketones such as 1-phenyl-1,3-butanedione **(1c)**, 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione



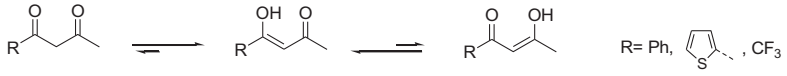
Scheme 4 Synthesis of 4-amino-5-benzoyl-6-phenyl-1*H*-pyridin-2-one (**5**).

(**1d**) and 1,1,1-trifluoropentane-2,4-dione **(1e)** exist mainly in two enol forms (Scheme 2). Based on the ^{1}H NMR and ^{13}C NMR only one product was obtained from the nucleophilic reaction of malononitrile on the acetyl group of unsymmetrical, 1,3-diketones **1c** and **1d**, however the reaction of 1,1,1-trifluoropentane-2,4-dione **(1e)** with malononitrile **(2)** in the same reaction condition afforded the mixture of 2-pyridinone **3(I)e** and **3(II)e** in different yields. Quantitative analysis of mixtures is achieved by evaluating the integration peaks of ^{1}H NMR spectrum ((**3(II)e**: 85% and **3(I)e**: 15%)).

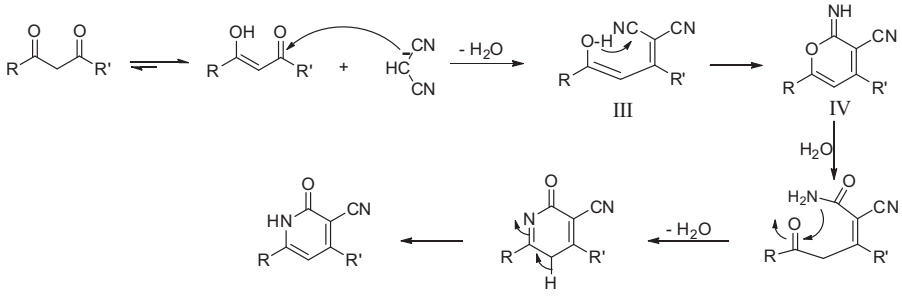
On the basis of our results, a plausible mechanism has been proposed for the reactions of 1,3-diketones (**1a–e**) with malononitrile to yield 3-cyano-2-pyridinone derivatives (**3a–e**), as shown in Scheme 3. The Knoevenagel reaction occurs via an initial formation of 4-oxo-ylidene malononitrile derivatives (**III**), from the condensation of malononitrile on the active carbonyl group of 1,3-diketones (**1a–e**). The second step is followed by intramolecular nucleophilic addition of the hydroxyl group on the cyano (CN) moiety, giving intermediate (**IV**). The final step



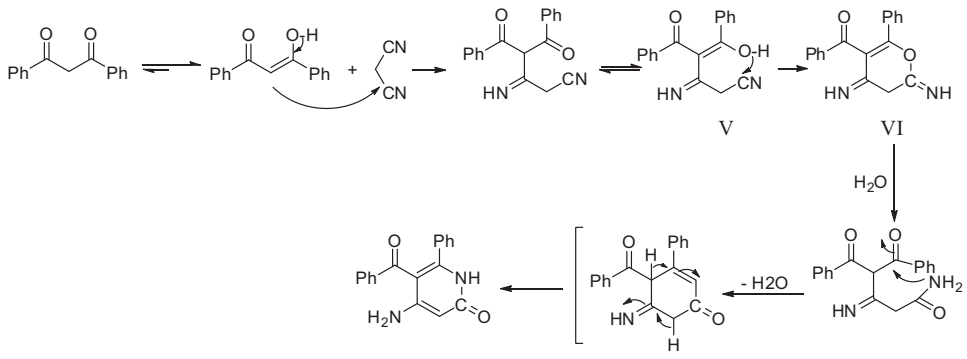
Scheme 1 Synthesis of 3-cyano-2-pyridinone derivatives (**3a–e**).



Scheme 2 Unsymmetrical 1,3-diketones in two enol forms.



Scheme 3 A mechanism for the formation of 3-cyano-2-pyridinone derivatives.



Scheme 5 A mechanism for the formation of 4-amino-5-benzoyl-6-phenyl-1*H*-pyridin-2-one.

is followed by nucleophilic addition of water, cycloaddition, isomerization to afford the 3-cyano-2-pyridinone derivatives (**3**).

In our investigation it was found that the reaction of dibenzoylmethane **4** with malononitrile **2** in the presence of a little amount of water gave 4-amino-5-benzoyl-6-phenyl-1*H*-pyridin-2-one **5** as the only product (Scheme 4).

The unexpected formation of the compound **5** can be explained as follows. We believe that the carbonyl group of dibenzoylmethane **4** is not as reactive as the other 1,3-dicarbonyl groups such as compounds (**1a–e**). It is pertinent to note that the methylene group of dibenzoylmethane **4** is a very reactive nucleophile compared to malononitrile. Therefore it is considered that this reaction proceeds by an initial nucleophilic attack of the β-carbon atom of the enol tautomer of dibenzoylmethane **4** on the nitrile group of malononitrile **2**, followed by intramolecular nucleophilic addition of the hydroxyl group to other nitrile groups of intermediate **V**. Similarly, nucleophilic addition of water on intermediate **VI** along with cycloaddition, isomerization leads to the formation of 4-amino-5-benzoyl-6-phenyl-1*H*-pyridin-2-one **5** (Scheme 5).

3. Conclusions

In summary, we have developed a simple method to synthesize a series of fluorinated pyridinones via the reaction of 1,3-diketones with malononitrile, the desired products were obtained with up to 85% yields in ethanol at reflux and in short experimental times. Also this methodology offers a different route for the synthesis of 4-amino-5-benzoyl-6-phenyl-1*H*-pyridin-2-one. Synthesis of 4-amino-2-pyridinone would be achieved because the amine partners can be flexibly varied. Owing to the interest of the amino-2-pyridinone derivatives for the design of biologically relevant compounds.

4. Experimental section

Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FT-IR spectrometer. The proton and carbon NMR spectra were recorded with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

*4.1. General procedure for the preparation of 3-cyano-2-pyridinones (**3a–e**)*

A mixture of β-dicarbonyl **1a–e** (2 mmol), malononitrile **2** (2 mmol) and triethylamine (0.2 ml) in ethanol (20 mL) was refluxed with stirring for 15 min (the progress of the reaction being monitored by TLC and used hexane/ethyl acetate as an eluent). When the reaction was completed as indicated by TLC, the crude product **3a–e** was precipitated from the reaction mixture by cooling, and the solid was filtered and recrystallized with ethanol to get the pure product.

*4.2. General procedure for the preparation of 4-amino-5-benzoyl-6-phenyl-1H-pyridin-2-one (**5**)*

A mixture of dibenzoylmethane **4** (2 mmol) and malononitrile **2** (2 mmol), in CH_2Cl_2 (20 mL) was refluxed with stirring for 15 min (the progress of the reaction being monitored by TLC and used hexane/ethyl acetate as an eluent). Then 2 ml H_2O was added to the mixture reaction and refluxed with stirring for 10 min. When the reaction was completed as indicated by TLC, the crude product **5** was precipitated from the reaction mixture by cooling, and the solid was filtered and recrystallized with ethanol to get the pure product.

4.3. Spectral data for selected compounds

*4.3.1. 1,2-Dihydro-4,6-dimethyl-2-oxopyridine-3-carbonitrile (**3a**)*

Yield: 95%. m.p. 276–278 °C (decompose); IR (KBr, vmax/cm^{-1}): 3341 (NH), 2216 (CN), 1670 (C═O), 1620, 1580 (C═C); ^{1}H NMR (500 MHz, DMSO-d6): 8.40 (s, 1H, NH), 6.07 (s, 1H), 2.34 (s, 3H, CH_3), 2.23 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d6): 160.87 (C═O), 159.75 (C_6), 150.84 (C_4), 115.79 (CN), 115.40 (C_3), 106.31 (C_5), 20.65, 18.25 (2 CH_3); MS (*m*/*z*): 148 (M^+) (100), 120 (35), 119 (80), 105 (20). Anal. Calcd. For $C_8H_8N_2O$: C, 64.72; H, 5.46; N, 18.97%. Found: C, 64.85; H, 5.44; N, 18.91.

*4.3.2. 4,6-Bis(trifluoromethyl)-1,2-dihydro-2-oxopyridine-3-carbonitrile (**3b**)*

Yield: 85%. m.p. 123–125 °C; IR (KBr, vmax/cm^{-1}): 3340 (NH), 2216 (CN), 1660 (C═O), 1620, 1580 (C═C); ^{1}H NMR (500 MHz, DMSO-d6): 8.89 (s, 1H, NH), 6.24 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d6): 155.40 (C_4), 150.23 (C═O), 135.75 (C_6), 112.59 (q, $^1J_{C\text{-}F}$, 284.25 Hz, CF_3),

112.44 (q, $^{1}J_{C\text{-}F}$, 276.25 Hz, CF_3), 110.21 (C_3), 110.12 (CN), 108.31 (C_5); MS (*m*/*z*): 256 (M^+) (5), 251 (70), 198 (100), 182 (60), 117 (10), 93 (10), 75 (10), 69 (50).

*4.3.3. 1,2-Dihydro-4-methyl-2-oxo-6-phenyl pyridine-3-carbonitrile (**3c**)*

Yield: 92%; m.p. 285 °C (decompose); IR (KBr, νmax/cm^{-1}): 3255 (NH), 2212 (CN), 1617 (C═O), 1590, 1492 (C═C); ^{1}H NMR (500 MHz, DMSO-d6): 12.43 (s, 1H, NH), 7.69–7.41 (m, 5H, Ar), 6.63 (s, 1H), 2.40 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d6): 162.26 (C═O), 161.13 (C_6), 151.32 (C_4), 133.00, 131.90, 129.79, 128.33, 116.80 (C_3), 115.12 (CN), 107.91 (C_5), 21.62 (CH_3); MS (*m*/*z*): 210 (M^+) (5), 196 (80), 185 (20), 171 (10), 134 (20), 95 (100), 77 (40), 45 (60). Anal. Calcd. For $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32%. Found: C, 74.35; H, 4.74; N, 13.37.

*4.3.4. 4-(Trifluoromethyl)-1,2-dihydro-2-oxo-6-(thien-2-yl)pyridine-3-carbonitrile (**3d**)*

Yield: 88%; m.p. 205–208 °C; IR (KBr, νmax/cm^{-1}): 3404 (NH), 2237 (CN), 1641 (C═O), 1592, 1567 (C═C); ^{1}H NMR (500 MHz, DMSO-d6): 8.90 (s, 1H, NH), 7.83 (d, 1H, $^{3}J_{H\text{-}H}$ = 5.03 Hz, CH), 7.72 (d, 1H, $^{3}J_{H\text{-}H}$ = 3.67 Hz, CH), 7.20–7.18 (m, 1H, Ar), 7.08 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d6): 160.40 (C_4), 155.68 (C═O), 143.77 (C_6), 136.04, 131.84, 131.31, 129.49, 122.74 (q, $^{1}J_{C\text{-}F}$, 273.25 Hz, CF_3), 114.37 (C_3), 114.12 (CN), 98.18 (C_5); MS (*m*/*z*): 270 (M^+) (8), 246 (15), 193 (20), 148 (40), 106 (80), 91 (100), 77 (20), 57 (85). Anal. Calcd. For $C_{11}H_5F_3N_2OS$: C, 48.89; H, 1.86; N, 10.37%. Found: C, 52.59; H, 1.88; N, 14.17.

*4.3.5. Trifluoromethyl-methyl-2-oxopyridine-3-carbonitrile (**3e**)*

Yield: 90%; m.p. 160 °C (decompose); IR (KBr, νmax/cm^{-1}): 3354 (NH), 2237 (CN), 1666 (C═O), 1617, 1567 (C═C); MS (*m*/*z*): 202 (M^+) (10), 188 (70), 163 (30), 134 (15), 109 (100), 95 (60), 45 (40). Anal. Calcd. For $C_8H_5F_3N_2O$: C, 47.54; H, 2.49; N, 13.86%. Found: C, 48.40; H, 2.48; N, 14.01. *6-Trifluoromethyl-1,2-dihydro-4-methyl-2-oxopyridine-3-carbonitrile* (**3(I)e**): ^{1}H NMR (500 MHz, DMSO-d6): 13.35 (s, 1H, NH), 6.64 (s, 1H), 2.28 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d6): 161.36 (C═O), 151.15 (C_4), 146.86 (C_6), 124.10 (q, $^{1}J_{C\text{-}F}$, 262.5 Hz, CF_3), 115.89 (C_3), 114.27 (CN), 102.44 (C_5), 21.91 (CH_3). *4-(trifluoromethyl)-1,2-dihydro-6-methyl-2-oxopyridine-3-carbonitrile* (**3(II)e**): ^{1}H NMR (500 MHz, DMSO-d6): 8.36 (s, 1H, NH), 7.12 (s, 1H), 2.38 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d6): 157.75 (C_4), 154.49 (C═O), 146.61 (C_6), 121.50 (q, $^{1}J_{C\text{-}F}$, 274.50 Hz, CF_3), 115.85 (C_3), 114.19 (CN), 101.34 (C_5), 20.41 (CH_3).

*4.3.6. 4-Amino- 5-benzoyl-6-phenyl-1H-pyridin-2-one (**5**)*

Yield: 88%; m.p. 290 °C; IR (KBr, νmax/cm^{-1}): 3478, 3344, 3304 (NH, NH_2), 1720 (Ph-C═O), 1641 (NH-C═O), 1617, 1592 (C═C); ^{1}H NMR (500 MHz, DMSO-d6): 10.31 (s, 1H, NH), 8.90 (s, 2H, NH_2), 7.40–6.025 (m, 10H, Ar), 5.93 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d6): 197.10 (Ph-C═O), 160.53 (NH-C═O), 158.44 (C_4), 147.93 (C_6), 136.13, 133.72, 130.02, 129.74, 129.48, 129.28, 128.85, 128.81, 124.86 (C_5), 109.07 (C_3); MS (*m*/*z*): 290 (M^+) (15), 261 (18), 221 (10), 146 (8), 105 (80), 91 (15), 77 (100), 58 (25), 51 (35). Anal. Calcd. For $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33%. Found: C, 72.02; H, 3.98, N, 13.05.

Acknowledgements

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